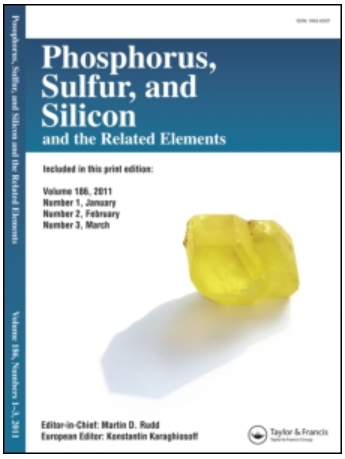

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

N-ALKYL-N-PHOSPHONOMETHYLENE-AMINOMETHYL PHOSPHINIC ACIDS

Roman Tyka[a]; Gerhard Hägele[b]; Jürgen Peters[b]
[a] Institute of Organic and Physical Organic Chemistry, Technical University (Politeknika), Wyb., Wispianskiego, Poland [b] Institut für Anorganische Chemie und Strukturchemie I, Universität Düsseldorf, üsseldorf, G.F.R.

To cite this Article Tyka, Roman , Hägele, Gerhard and Peters, Jürgen(1987) 'N-ALKYL-N-PHOSPHONOMETHYLENE-AMINOMETHYL PHOSPHINIC ACIDS', Phosphorus, Sulfur, and Silicon and the Related Elements, 34: 1, 31 — 37
To link to this Article: DOI: 10.1080/03086648708074304
URL: http://dx.doi.org/10.1080/03086648708074304

Phosphorus and Sulfur, 1987, Vol. 34, pp. 31–37
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ROMAN TYKA

Institute of Organic and Physical Organic Chemistry, Technical University (Politeknika), P-50-370 Wrocław, Wyb. Wispianskiego 27, Poland

GERHARD HÄGELE and JÜRGEN PETERS

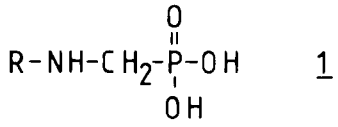
Institut für Anorganische Chemie und Strukturchemie I, Universität Düsseldorf Universitätsstrasse 1, D-4000 Düsseldorf, G.F.R.

(Received February 2nd 1987; in final form March 18, 1987)

The new compounds, R—N($CH_2PO_3H_2$)CH_2P(R')O_2H **3** (R = Me, Et, nPr, nBu, $PhCH_2$; R' = Me, Et, Ph) are synthesized using a combination of previously reported and the MOEDRITZER reaction sequences.

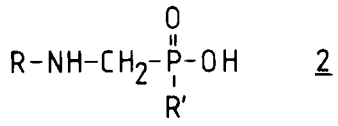
INTRODUCTION AND RESULTS

Aminophosphonic acids **1**



1

and aminophosphinic acids **2**

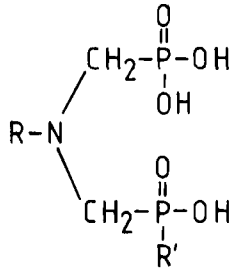


2

are of considerable theoretical and practical interest. Very recently a comprehensive review has reported a broad variety of herbicidal, antimicrobial and neuroactive species.[1] In preceding papers[2] we have described convenient synthetic routes leading to N-alkyl-aminomethyl-P-alkyl- and aryl-phosphinic acids **2**, based on easily accessible precursors, such as *n*-alkylformamides, paraformaldehyde and dichlorophosphines. In continuation of our studies we have searched for model systems similar to glyphosphate, well known for its plant growth accelerating properties.

We have found that phosphonomethylation, using the MOEDRITZER method,[3] of N-alkyl-amino-methyl-P-alkyl- and aryl-phosphinic acids **2** lead to the hitherto unknown N-alkyl-N-phosphonomethylene-aminomethyl-P-alkyl- and

aryl-phosphinic acids **3**



3

as described by the following reaction sequences:

$$\text{R—NH—CHO} \xrightarrow[K_2CO_3]{(CH_2O)_x} \text{R—N(CHO)CH}_2\text{OH} \qquad (1)$$

4 **5**

R	Me	Et	nPr	nBu	$PhCH_2$
	4a	**4b**	**4c**	**4d**	**4e**
	5a	**5b**	**5c**	**5d**	**5e**

$$\mathbf{5} + \xrightarrow[-2HCl,\ -HCOOH,\ (in\ CH_3COOH)]{1)+R'PCl_2\,6/2)+2H_2O} \text{R—NH—CH}_2\text{—P(R')O}_2\text{H} \qquad (2)$$

7

R′	Me	Et	Ph
	6a	**6b**	**6c**
	7a	**7b**	**7c**

$$\mathbf{7} + \xrightarrow[-H_2O\ (in\ 20\%\ HCl)]{+CH_2O+H_3PO_3} \mathbf{3} \qquad (3)$$

R		Me	Et	nPr	nBu	$PhCH_2$
R′	Me	**3a**	**3b**	**3c**	**3d**	**3e**
	Et	**3f**	**3g**	**3h**	**3i**	**3j**
	Ph	**3k**	**3l**	**3m**	**3n**	**3o**

The isolation of chemically pure and crystalline products **3a–3o** is not trivial. Compounds **3e** and **3j–3o**, with phenyl or benzyl substituents, crystallized readily after purification by means of an ion-exchange column. The remaining compounds, **3a–3d** and **3f–3i**, bearing alkyl substituents only, had to be recrystallized repeatedly from methanol-water- or acetone-water-mixtures in order to obtain chemically pure compounds.

We have isolated **3b–3d**, **3f** and **3q** in a crystalline state but **3a**, **3h** and **3i** in

TABLE I

Yields (%) and melting points (°C) of compounds **3a–3o**

Comp.	Yield (%)	m.p. (°C)	Solvent used for crystallisation
3a	37	—	a
3b	32	177–178	a
3c	39	195–198	b
3d	42	164–166	c
3e	51	195–198	d
3f	46	193–195	d
3g	42	175–178	
3h	35	—	
3i	39	—	
3j	65	215–217	b
3k	55	234–236	d
3l	58	225–227	c
3m	59	189–191	c
3n	52	212–213	c
3o	66	230–233	e

Solvents used for crystallisation: a) methanol, b) ethanol–water, c) acetone–water, d) methanol–water, e) see text.

amorphous forms only. These results are summarized in Table I. All products were identified by elemental analysis (N, P), IR- and NMR-spectroscopy. Results from more detailed NMR investigations will be published elsewhere.

EXPERIMENTAL

Melting points were determined using a Boethius apparatus and were not corrected. The IR spectra were taken on a Perkin–Elmer 621 instrument, 60 MHz ^{1}H-NMR spectra were recorded with a TESLA BS 467 instrument operating at the Wrocław Institute. 200 MHz ^{1}H-NMR spectra were obtained, using the Bruker AM 200 spectrometer and 36.4 MHz ^{31}P{^{1}H}-NMR spectra were run on a Bruker HX 90 R spectrometer in Düsseldorf. TMS and 85% H_3PO_4 were used as external references for ^{1}H and ^{31}P chemical shift data. Positive values for relative resonance frequencies correspond to positive chemical shift data.

Comments on N-Alkylformamides, ***4a–4e***

For synthesis and physical data see Reference 4. Modifications: 1 mole of amine is dissolved slowly in 2.5 moles of formic acid. After refluxing the reaction mixture for 30 min the volatile products are removed using a rotary evaporator. The remaining N-alkylformamide is fractionated in vacuo.

N-Alkyl-N-hydroxymethylformamides, ***5a–5e***

A mixture of N-alkylformamide, **4a–4e**[3] (0.2 mole), paraformaldehyde (6 g; 0.2 mole) and anhydrous potassium carbonate (0.2 g) is heated to 90–100°C until all the paraformaldehyde is dissolved (30 min). After cooling this crude product is used directly without further purification in the subsequent condensation step.

N-Alkyl-aminomethyl-P-alkyl-and-aryl-phosphinic acids, ***7a–7o****. General Procedure*

N-Alkyl-N-hydroxymethylformamide, **5a–5e** (0.2 mole) in glacial acetic acid (30 ml) is added slowly with stirring and cooling (cold water) to the alkyl- or aryldichlorophosphine, **6a–6c** (0.15 mole). After strirring for 15 min the mixture is heated under reflux for 30 min, treated with 20% hydrochloric acid (40 ml) and refluxed for another 30 min. Volatile products are evaporated in vacuo, the remaining residue is dissolved in methanol (20–40 ml), and treated with propylene oxide (HCl scavenger) until

TABLE II

^{31}P chemical shift data (ppm) of phosphinic and phosphonic groups for solutions of compounds **3a–3o** dissolved with concentrations (mol/l) as specified above. Solvent: 1.0 molar solution of KOH in D_2O.

Comp.	Concentration of solution (mol/l)	Phosphorus chemical shift data Phosphinic group	Phosphonic group
3a	0.289	39.48	15.25
3b	0.072	40.28	15.92
3c	0.068	40.36	16.00
3d	0.067	40.39	15.97
3e	0.081	40.98	15.97
3f	0.100	43.04	15.30
3g	0.067	43.71	15.94
3h	0.084	43.97	16.02
3i	0.079	43.82	16.05
3j	0.061	44.35	16.08
3k	0.063	29.21	15.41
3l	0.046	29.88	16.08
3m	0.048	29.88	16.21
3n	0.042	29.88	16.24
3o	0.124	30.36	16.16

TABLE IIIa

200 MHz ^1H—NMR data for the methylene protons in the $^-O_2(R')P—CH_2—N—CH_2—PO_3^{2-}$ fragment of compounds **3a–3o**. Chemical shift data given in ppm vs. external 85% H_3PO_4 and coupling constants $^2J_{PH}$ (in parentheses) given in Hz. Solutions as specified in Table II

Comp.	$^-O_2(R')P—CH_2—N$ δ_H	$^2J_{PH}$	$N—CH_2—PO_3^{2-}$ δ_H	$^2J_{PH}$
3a	2.75	(−9.51)	2.59	(−11.45)
3b	2.84	(−8.75)	2.68	(−11.30)
3c	2.84	(−9.71)	2.66	(−11.19)
3d	2.82	(−9.86)	2.64	(−11.49)
3e	2.77	(−9.86)	2.70	(−11.53)
3f	2.73	(−9.15)	2.58	(−11.40)
3g	2.83	(−9.60)	2.69	(−11.38)
3h	2.85	(−9.35)	2.70	(−11.35)
3i	2.85	(−9.56)	2.70	(−11.26)
3j	2.73	( )	2.73	(−11.78)
3k	2.96	(−8.84)	2.53	(−11.32)
3l	3.07	(−9.89)	2.65	(−11.33)
3m	3.09	(−9.95)	2.66	(−11.32)
3n	3.11	(−9.10)	2.56	(−11.25)
3o	3.03	(−9.32)	2.75	(−11.22)

TABLE IIIb

200 MHz ^{1}H-NMR data for the R′-PO_2^- groups of compounds **3a–3o**. Chemical shift data given in ppm vs. external TMS and coupling constants given in Hz. Solutions as specified in Table II

R′ = CH_3					
3a	**3b**	**3c**	**3d**	**3e**	Parameter
1.26	1.30	1.24	1.22	1.16	$\delta_H CH_3$
−13.34	−13.37	−13.30	−13.28	−13.39	$^2J_{PH}$
R′ = CH_3CH_2[a]					
3f	**3g**	**3h**	**3i**	**3j**	Parameter
1.43	1.46	1.46	1.46	1.34	$\delta_H CH_3$ (l)
1.62	1.64	1.61	1.61	1.51	$\delta_H CH_3$ (u)
0.92	0.93	0.94	0.93	0.71	$\delta_H CH_2$ (l)
0.94	1.09	1.10	1.10	0.87	$\delta_H CH_2$ (u)
R′ = Ph					
3k	**3l**	**3m**	**3n**	**3o**	Parameter
7.51	7.51	7.51	7.47	7.18	δ_HPh (l)
7.78	7.79	7.79	7.80	7.61	δ_HPh (u)

[a] $^2J_{PH} = -12$ Hz, $^3J_{PH} = 14$ Hz for **3f–3j**.
(l) and (u): lower and upper δ_H limits of multiplet structures observed.

TABLE IIIc

200 MHz ^{1}H-NMR data for the R–N groups of compounds **3a–3o**. Chemical shift data given in ppm vs. external TMS and coupling constants (in parenthesis) given in Hz. Solutions as specified in Table II

Comp.	Protons attached to carbon atoms of type: α	β	γ	δ	Phenyl
3a	2.46	—	—	—	—
3b	2.84	1.01	—	—	—
3c	2.69	1.45	0.81	—	—
3d	2.72	1.41	1.23	0.83	—
3e	3.92	—	—	—	7.31–7.51
3f	2.45	—	—	—	—
3g	2.83	0.93–1.09	—	—	—
3h	2.73	1.42–1.61	0.84	—	—
3i	2.76	1.46–1.61	1.25	0.88	—
3j	3.91	—	—	—	7.31–7.51
3k	2.37	—	—	—	—
3l	2.74	0.83	—	—	—
3m	2.57	1.23	0.60	—	—
3n	2.56	1.15	0.95	0.70	—
3o	3.81	—	—	—	7.18–7.61

Conventional indices (α, β, γ, δ) were used to locate the protons attached to carbon atoms in the H—$(CH_2)_n$—N, ($n = 1-4$), and Ph—CH_2—N units of the R–N groups.

TABLE IV

Molecular formulas, weights and data from elemental analyses of compounds **3a–3o**. Results are given in % Phosphorus and % Nitrogen for experimental (exp.) and calculated (calc.) data

Comp.	Molecular formula $C_iH_kO_5NP_2$ i	k	weight	% Phosphorus exp. (calc.)	% Nitrogen exp. (calc.)
3a	4	13	217.15	P 28.9 (28.6)	N 6.3 (6.4)
3b	5	15	231.17	P 26.7 (26.8)	N 6.4 (6.1)
3c	6	17	245.20	P 25.5 (25.3)	N 5.8 (5.7)
3d	7	19	259.23	P 24.2 (23.9)	N 5.4 (5.4)
3e	10	17	293.24	P 21.0 (21.1)	N 5.1 (4.8)
3f	5	15	231.17	P 27.1 (26.8)	N 6.2 (6.1)
3g	6	17	245.20	P 25.2 (25.3)	N 6.0 (5.7)
3h	7	19	259.24	P 24.2 (23.9)	N 5.5 (5.4)
3i	8	21	273.25	P 22.6 (22.7)	N 5.4 (5.1)
3j	11	19	307.27	P 20.1 (20.2)	N 4.9 (4.6)
3k	9	15	279.22	P 22.5 (22.2)	N 5.2 (5.0)
3l	10	17	293.24	P 21.1 (21.1)	N 4.7 (4.8)
3m	11	19	307.27	P 20.4 (20.2)	N 4.6 (4.6)
3n	12	21	321.30	P 19.6 (19.3)	N 4.7 (4.4)
3o	15	19	355.31	P 17.2 (17.4)	N 4.2 (3.9)

TABLE V

Wave numbers (cm^{-1}) for relative maxima of infrared absorptions of compounds **3a–3o** (KBr-pellets)

Comp.	Wave numbers (cm^{-1}) for relative maxima of infrared absorptions:
3a	3700–2000, 1650, 1470, 1310, 1130, 1050, 930, 750, 700, 530
3b	3600–2000, 1470, 1310, 1250, 1180, 1140, 1070, 1020, 920, 880, 750, 720, 590
3c	3600–2000, 1410, 1310, 1180, 1060, 930, 870, 790, 760, 720, 590, 510, 480, 460, 440, 410
3d	3700–2000, 1480, 1460, 1300, 1210, 1170, 1130, 950, 880, 750, 720, 710, 570, 430
3e	3600–2000, 1490, 1450, 1430, 1300, 1260, 1140, 950, 930, 870, 810, 750, 700, 600, 560, 500
3f	3700–2000, 1490, 1450, 1410, 1330, 1260, 1190, 1150, 1110, 770, 540, 470, 450, 420, 370
3g	3600–1950, 1670, 1480, 1370, 1200, 1080, 1020, 950, 840, 790, 770, 610, 540, 510, 470
3h	3700–2000, 1710, 1460, 1170, 1050, 930, 820, 770, 710, 500, 460
3i	3700–2000, 1640, 1460, 1400, 1170, 1050, 930, 770, 710, 550, 460
3j	3600–2000, 1460, 1420, 1260, 1120, 950, 750, 700, 600
3k	3600–2000, 1590, 1440, 1260, 1160, 1100, 1040, 950, 840, 740, 650
3l	3600–2000, 1440, 1260, 1170, 1130, 950, 740, 690
3m	3600–2000, 1650, 1470, 1440, 1420, 1250, 1160, 1130, 1050, 990, 740, 690
3n	3600–2000, 1430, 1220, 1190, 1120, 950, 880, 850, 770, 720, 690, 570, 550
3o	3600–2000, 1500, 1450, 1430, 1320, 1280, 1230, 1190, 1160, 1130, 1080, 950, 810, 750, 710, 690, 660, 580, 480

the pH-value of the resulting solution remains unchanged. Acetone is added until precipitation ceases. The precipitate is filtered, washed with acetone and dried in vacuo.

*N-Alkyl-N-phosphonomethylene-aminomethyl-P-alkyl- and -aryl-phophinic acids, **3a–3o**.*
General Procedure

A mixture of N-alkyl-aminomethylene-P-alkyl- or -aryl-phosphinic acid, **7a–7o** (0.02 mole), phosphorous acid (0.8 g; 0.025 mole), 3 ml 40% formaline and 7 ml 20% hydrochloric acid is heated under reflux for 2 h. Volatile products are evaporated using a rotary evaporator. The residue is dissolved in methanol (20 ml) and treated with propylene oxide until the pH values remains unchanged. Acetone

is added until precipitation ceases. In most cases the product is isolated as an oil. Then the resulting product is dissolved in a few ml of water, transferred to a Dowex 50WX8, 50–100 mesh column and eluated with water, collecting fractions of pH < 7. Water is stripped off under reduced pressure. The residue is mixed with methanol. The crystalline product formed is isolated by suction and dried. In cases where oily products are isolated at this stage, repeated crystallisations from methanol-water or acetone-water mixtures are required. See text and Table I. Compound **4o** is purified by dissolution in 5% NaOH and reprecipitation with 5% HCl.

ACKNOWLEDGEMENT

Thanks are due to Deutsche Forschungsgemeinschaft for financial support.

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